(FILE 'HOME' ENTERED AT 13:33:32 ON 16 OCT 2000)

```
FILE 'MEDLINE, BIOSIS, CAPLUS, EMBASE, LIFESCI, SCISEARCH, TOXLINE, BIOTECHNO, CANCERLIT, ESBIOBASE' ENTERED AT 13:33:43 ON 16 OCT 2000
                                                                                                                                              7 DUP REM L3 (24 DUPLICATES REMOVED)
66589 S (THREE (M) DIMENSIONAL (M) STRUCTUR?) OR (3D (M) STRUCTUR?)
0 S L1 AND L2 AND L5
13789 S L5 AND ((CRYSTAL OR X-RAY OR (X(M)RAY)) (3M) STRUCTUR?)
18 S L1 AND L3 AND ((CRYSTAL OR X-RAY OR (X(M)RAY)) (3M) STR
                                                                                                                                                                                                                                                                                                                                                                                                            4033 S IMPDH OR (INOSINE (W) MONOPHOSPHATE (W) DEHYDROGENASE?) OR, (I
                                                                                                                                                                                                                                                                                                                                                                                     24 S PYOGENES AND L1
                                                                                                                                                                                                                                                                                                                                                31'S L1 AND (STREPTOCOC? OR PYOGENES)
                                     S L4 AND L7
S L4 AND ((CRYSTAL OR X-RAY OR (X(W)RAY)) (3W) STRUCTUR?)
                                                                                                                DUP REM L8 (15 DUPLICATES REMOVED)
DUP REM L11 (0 DUPLICATES REMOVED)
                                                                                                                                                     (X(W)RAY)) (3W) STRUCTU
                                                                                                                                                                                                                                                                     (W) STRUCTUR?)
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  CABA,
                                                                                                                                                                                                                                                                     0
```

11 12 13 14 15 16 16 17 17 18 19 110

PA PA

TRR 44

```
AU 9915022
PRAI US 1997-997758
                                                                                                                                                                                                                                                                                                                CNT
                    of exogenous guanosine as a control component of the methods allows for
                                                                                                                                    This invention relates to methods to identify specific inhibitors of the
                                                                                                                                                                                                                                                                               WO-9933996
                               the pJFl18EH expression vector. A variety of eukaryotic or prokaryotic host systems commonly used for the expression. . . prodn. Utilizatic
                                                                                                  an essential enzyme found in all free-living organisms from humans to bacteria and is an important therapeutic target. The invention allows
                                                                                                                           purine nucleotide synthesis enzyme,
                                                                                                                                                   WO 1998-IB2109
                                                                                                                                                                                                                                                                                                   PATENT NO.
                                                                                                                                                                                                                                                                                                                         English
                                                                                                                                                                                                                                                                                                                                                   PCT Int. Appl., 34 pp.
                                                                                                                                                                                                                                                                                                                                                                                Collart, Frank R.; Huberman, Eliezer
other causes of decreased cell proliferation.
                                                                  illustrate the utility of the invention, the coding sequence of human and
                                                                             can be expressed in a functional form in a recombinant host cell.
                                                                                                                                                                                                                                                                                                                                     Patent
                                                                                                                                                                                                                                                                                                                                                CODEN: PIXXD2
                                                                                                                                                                                                                                                                                                                                                                     The University of Chicago, USA
                                                                                                                                                                                                                                                                                                                                                                                                     Method to identify specific inhibitors of
                                                                                                                                                                                                                                                                                                                                                                                                                                         ANSWER 1 OF 7 CAPLUS COPYRIGHT 2000 ACS
                                                                                        identification of specific inhibitors of any
                                                                                                                                                                                                                                                                                                                                                                                                                  131:83979
                                                                                                                                                                                                                                                                                                                                                                                                                             1999:464100
                                                       * * *Streptococcus * * *
                                                                                                                                                                                                                                                                                                                                                                                           ***monophosphate***
                                                                                                                                                                                               T 9
                                                                                                                                                                                     8
                                                                                                                                                                                                                     TR,
                                                                                                                                                                                                                                 ¥
                                                                                                                                                                                              EE, KG, EE, FR, GM,
                                                                                                                                                                                     GA,
                                                                                                                                                                                  GB,
                                                                                                                                                                                                                                ES,
NO,
                                                                                                                                                                                                                                                                                                    KIND
                                                                                                                                                              19971224
                                                                                                                                                    19981223
                                                                                                                                                                                                                                                                               2
                                                                                                                                                                                  GR, GR,
                                                                                                                                                                                                                                FI,
KR,
NZ,
                                                                                                                                                                                                                               19990708
, AZ, BA,
, GB, GD,
, KZ, LC,
, PL, PT,
                                                                                                                                                                                                                                                                                                    DATE
                                                                                                                                                                                                                                                                                                                                                                                         ***dehydrogenase***
                                                      ***pyogenes***
                                                                                                                                                                                  ¥
                                                                                                                                                                                                                      Š
                                                                                                                                                                                                                                RO, GE,
                                                                                                                                                                                    NE C
                                                                                                                                                                                                                     ď
                                                                                                                                                                                 BG, BR, GH, GM, LR, LS, RU, SD, ZW, AM, UG, ZW, MC, NL, SN, TD,
                                                                                                                                                                                                                                                                  WO 1998-IB2109
5, BR, BY, CA, (
                                                                                                                        ***HDDH***
                                                                                                                                                                        AU 1999-15022
                                                                                                                                                                                                                                                                                                   APPLICATION NO.
                                                                                                                                                                                                                                                                                                                                                                                                      ***inosine***
                                                                                                                                                                                     G
                                                                                                                                                                                                            SE,
AZ,
                                                                                                                                                                                                                                                       Ħ,
                                                       * * * IMPDH * * *
                                                                                          * * * IMPDH * * *
                                                                                                                                                                                               SE,
                                                                                                                                                                                                                     SG,
           * * * IMPDH * * *
                                                                                                                                                                                                                                             'n
                                                                                                    The invention allows the
                                                                                                                                                                                               B C K
                                                                                                                                                                                                                                ID,
SI,
                                                                                                                                                                                                                                                                  臼,
                                                                                                                                                                                                                                                     19981223
, CN, CU,
, IL, IN,
                                                                                                                                                                         19981223
                                                                                                                                                                                               B C K
                                                                                                                           * * * IMPDH * * *
                                                                                                                                                                                                                                 SK,
                                                                                                                                                                                                                                             Ğ,
                                                       were cloned into
                                                                                                                                                                                               CF,
                                                                                       enzyme which
           rather than
                                                                                                                                                                                               ឧ
                                                                                                                                                                                                                                J K IS
                                                                              ö
                                                                                                                                                                                               CI,
                                                                                                                                                                                                                                 M A A E
                                                                                                                           15
                                                                                                                                                                                                                       덮
```

SO AU

Differential signatures of bacterial and mammalian

enzymes.

***dehydrogenase**

CURRENT MEDICINAL CHEMISTRY, (1999 Jul) 6 (7) 537-43.

Journal code: CO2. ISSN: 0929-8673

Differential signatures of bacterial and mammalian ***dehydrogenase*** enzymes.

ANSWER 4 OF 7 MEDLINE

Zhang R; Evans G; Rotella F; Westbrook E;

Huberman E; Joachimiak A;

DUPLICATE 3

IMP

```
ΑU
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              SO
                                                                                                                                                                                                                                                                                                                                                                                               B II
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                Ð
                                                                                                                                                                                                                                                                                                          ***Inosine*** (**monophosphate*** ***dehydrogenase*** (
***IMPDH*** ) catalyzes the conversion of IMP to XMP with the concomitant reduction of NAD to NADH. This reaction is the rate-limiting step in
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        crystallographic 4-fold axis. The protein is composed of two domains:. flap as an essential catalytic element and indicate there are significant differences in the catalytic environment of bacterial and mammalian ***IMPDH**** enzymes. Comparison of the structure of
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       to ***IMPDH*** in a random order, hydride transfer is fast and NADH release precedes hydrolysis of E-XMP*. The hydrolysis of E-XMP* is.
                                        reminiscent of glyceraldehyde-3-phosphate dehydrogenase. Substrates bind
to ***IMPDH*** in a random order, hydride transfer is fast and NADH
                                                                                                     hydrolysis of a covalent enzyme intermediate (E-XMP*) in a reaction
                                                                                                                                       monovalent cations, and one monovalent cation binding site appears to have been identified. The mechanism of ***IMPDH*** involves formation and
                                                                                                                                                                                                           a target for antimicrobial agents.
                                                                                                                                                                                                                                                                                      guanine nucleotide biosynthesis.
                                                                                                                                                                                                                                                                                                                                                                                                                                                            Journal code: CO2. ISSN: 0929-8673
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    CURRENT MEDICINAL CHEMISTRY, (1999 Jul) 6 (7) 545-60. Ref: 89
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             Hedstrom L
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  Biology Center at Argonne's Advanced Photon Source. S.
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         synchrotron radiation from the undulator beamline (19ID) of the Structural
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      acid and the Km for NAD (1180 microM) exemplify some of the differences between the bacterial and mammalian ***IMPDH*** enzymes, making it an
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 results show that the biochemical and kinetic characteristics of S.
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          pathogenic bacterium
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     agents, we have expressed and characterized
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  BIOCHEMISTRY,
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             ANSWER 3 OF 7
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         properties and contribute to the design of specific bacterial
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              eukaryotic organisms will provide an explanation of their distinct
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    bacterial
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            these differences, we
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        attractive target for antimicrobial agents. To evaluate the basis for
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             Journal code: AOG. ISSN: 0006-2960
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    Joachimiak A; Collart F R
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               Zhang R; Evans G; Rotella F J; Westbrook E M; Beno D; Huberman
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                Characteristics and crystal structure of bacterial inosine-5'-
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     ANSWER 2 OF 7 MEDLINE
                                                                                                                                                                                                                                                 immunosuppressive, anticancer and antiviral chemotherapy, and may also be
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     monophosphate dehydrogenase.
                                                                                                                                                                                                                                                                                                                                                                                            ***Inosine***
                                                                                                                                                                                                                                                                                                                                                                                                                              ***IMP***
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  ***IMP***
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          * * * IMPDH * * *
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   ***pyogenes***
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    ***IMPDH***
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              inhibitors
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               (1999 Apr 13) 38 (15) 4691-700.
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             MEDLINE
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                is a tetramer with its four subunits related by a
                                                                                                                                                                                                                                                                                                                                                                                                                       ***dehydrogenase***
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              ***dehydrogenase*** : mechanism of action and inhibition.
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 enzymes. However, the lack of sensitivity to mycophenolic
                                                                                                                                                                                                                                                                                                                                                                                     ***monophosphate***
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      ***IMPDH***
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      determined the crystal. .
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       ***Streptococcus***
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             with the known partial structures from
                                                                                                                                                                                                                                                                                      * * * HDGMI * * *
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   are similar to other bacterial
                                                                                                                                                                                                           * * * IMPDH * * *
                                                                                                                                                                                                                                                                                                                                                                                                                       : mechanism of action and inhibition
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         inhibitors as antimicrobial ****IMPDH*** from the
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       ***pyogenes***
                                                                                                                                                                                                                                                                                  is a proven target for
                                                                                                                                                                                                               is activated by
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             DUPLICATE 2
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     DUPLICATE 1
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  obtained with
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  ***pyogenes***
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      To provide
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   (i)
```

of this enzyme phylogenetic groups. Elucidation of the basis for this mammalian/bacterial secondary pattern of amino acid conservation associated with process include regions involved in subunit interactions, the. mutagenesis. Candidate bacterial sequence signatures identified by this have a role in catalysis using information derived from the bacterial enzymes. These selections were further refined to discern those likely to signatures associated with bacterial or eukaryotic used sequence alignments of development characteristics that are different than the mammalian applications may be extended to the development of antimicrobial agents. agents. The essential nature of this enzyme suggests its therapeutic kinetic differences between. identification of agents that specifically target the bacterial enzyme. We used sequence alignments of ***IMPDH*** proteins to identify sequence * * * HMPMH * * * me of de novo guanine nucleotide synthesis. ***IMPDH*** inh: clinical utility as antiviral, anticancer or immunosuppressive * * * HDDH * * * of antimicrobial agents. and the foundation signature will provide insight into the catalytic mechanism *dehydrogenase*** ***IMPDH*** may be an attractive target for the crystal structures and site-specific enzymes show biochemical and kinetic for the development of highly specific. is a prerequisite for the rational We suggest that the biochemical and * * * HDDH * * * proteins to identify sequence ***) is an essential ***IMPDH*** inhibit *** IMPDH*** *** HMPMI *** the major inhibitors

IMPDH , E.C. 1.1.1.205) is recognized as an important target for both antileukemic and immunosuppressive therapy. ***IMPDH*** catalyze binding. Journal code: C02. ISSN: 0929-8673 CURRENT MEDICINAL CHEMISTRY, (1999 Jul) 6 (7) 519-36. ANSWER 5 OF 7 the NAD-dependent oxidation of inosine 5 monophosphate (IMP) to xanthosine Goldstein B M; binding. Colby T D MEDLINE ***dehydrogenase*** ***dehydrogenase*** ***monophosphate*** : structural aspects of inhibitor : structural aspects of inhibitor ***dehydrogenase*** DUPLICATE 4 Ref: 118 catalyzes

SO

TI

₽B Ξ

has led to the search for potential, many agents. Recently, a number of crystal structures of ***IMPDH*** have become available. These include structures of the human type II, hamster, and ***Strentococcus*** ***pyogenes*** and exists as two isoforms, one of which (type II) is induced in tumor cells, has led to the search for potentially more effective isoform-specific Borrelia burgdorferi enzymes. Each structure crystallizes as a tetramer of susceptibility to metabolic inactivation. The finding that SUDSTRATE SITE (e.g. ribavirin. . acid and chiazote-4-carboxamic adenine dinucleotide). All suffer from some degree of toxicity and/or substrate site (e.g. ribavirin. use or under development. These include agents that bind at either the monophosphate. Several classes of barrels, with the active site located partly at. . ***IMPDH*** acid and thiazole-4-carboxamide inhibitors are now in * * * IMPDH * * *

SO 14 T1 Cloning, sequence analysis and expression of the group A Cloning, sequence analysis and expression of ***streptococcal*** guaB gene encoding Journal code: FOP. ISSN: 0378-1119. Ashbaugh ANSWER 6 OF 7 MEDLINE ***streptococcal*** ***monophosphate*** (1995 Nov 7) 165 (1) 57-60 Wessels M R guaB gene encoding
dehydrogenase guaB gene encoding ***inosine*** the group A * * * inosine * * *

> ₽ protein of 493 amino acids. Expression of the GAS guaB in an Escherichia coli guaB mutant restored ***IMPDH*** activity, confirming the active in a heterologous bacterial. open reading frame similar to other bacterial guaB genes encoding cloned a group A function of the gene product and demonstrating that the GAS enzyme is ***IMPDH***) is an essential enzyme in the biosynthesis of purines. We loned a group A ***streptococcal*** (GAS) DNA fragment containing an * * * IMPDH * * * ***Inosine*** ***monophosphate*** The GAS guab consists of 1479 nucleotides encoding a ***monophosphate*** ***dehydrogenase*** ***dehydrogenase***

ANSWER 7 OF 7 CAPLUS COPYRIGHT 2000 ACS

11 54 A simple method for the rapid determination of the stereospecificity of NAD-dependent dehydrogenases applied to mammalian ***IMP***

Cooney, David; Hamel, Ernest; Cohen, Marvin; Kang, Gil J.; Dalal, Maha; ***dehydrogenase*** and bacterial NADH peroxidase

ΑU

ö Marquez, Victor
Biochim. Biophys. Acta (1987), 916(1), 89-93

A simple method for the rapid determination of the stereospecificity NAD-dependent dehydrogenases applied to mammalian

1.1.1.205) from 2 different sources was detd. The enzyme prepns. were obtained from murine lymphoblasts and from Escherichia coli...tl enzyme from 2 very different species. In addn., the studies described here demonstrated that alc. dehydrogenase and NADH peroxidase (The stereospecificity of ***dehydrogenase*** from 2 different sources was detd. and bacterial NADH peroxidase ***dehydrogenase***

AB

Ŧ

with a microdistn. procedure, may rapidly det. the stereospecificity of any NAD-dependent dehydrogenase. ***Streptococcus*** faecalis), used as auxiliary enzymes, in combination

SS LA CY 몿 1999322381 99322381 Priority Journals PDB-1ZFJ ANSWER 2 OF 3 199907 United States BIOCHEMISTRY, Fcollart@anl.gov Center for Mechanistic Biology and Biotechnology, Argonne National Zhang R; Evans G; Characteristics and 99218077 English Journal; Article; Journal code: Laboratory, Joachimiak A; Collart F R inosine-5'-monophosphate dehydrogenase. ANSWER 1 OF 3 .999218077 9700 South Cass Avenue, Argonne, MEDLINE MEDLINE AOG. MEDLINE MEDLINE (1999 Apr 13) 38 (15) 4691-700 Rotella F J; Westbrook E M; Beno D; Huberman E; (JOURNAL ARTICLE) ISSN: ***crystal*** 0006-2960. ***structure*** Illinois 60439-4833, USA... DUPLICATE 2 DUPLICATE of bacterial

dehydrogenase enzymes.
Zhang R; Evans G; Rotella F; Westbrook E; Huberman E; Joachimiak A; Differential signatures of bacterial and mammalian *** IMP***

```
PRAI
                                                                                                                                                S
                                                                                                                                                                                                                                Å
                                                                                                                                                                                                                                                         EW ES F
                                                                                                                                                                                                                                                                                                         검단
                                                                                                                                                                                                                                                                                                                                 S
                                                                                                                                                                                                                                                                                                                                                 CS
                                                                                                                                                                                                                                                                                                                                                                        II
                                                                                                                                                                                                                                                                                                                                                                                DN AN
                                                                                                                                                                                                                                                                                                                                                                                                                B & & B & B & B
                                                                                                                                                                                                                                d 1 14
WO
                                                                                                                 CNT
                                                                                        WO 9933996
                                                                                                                       English
                                                                                                                                                              Method to identify specific inhibitors of
***monophosphate***
***dehydrogenas
Collart, Frank R.; Huberman, Eliezer
                                                                                                                                                                                                                                                                                                                              Department of Biochemistry and Biophysics, University of Rochester Medical Center, Rochester, NY, 14642, USA. barry_goldstein@urmc.rochester.edu CURRENT MEDICINAL CHEMISTRY, (1999 Jul) 6 (7) 519-36. Ref: 118
                                                                                                        PATENT NO.
                                                                                                                                 Patent
                                                                                                                                        CODEN: PIXXD2
                                                                                                                                                                                                                                                                                English
                                                                                                                                                                                                                                                                                                 General Review;
                                                                                                                                               PCT Int. Appl., 34 pp.
                                                                                                                                                       The University of Chicago,
                                                                                                                                                                                                        ANSWER 1 OF 7
                                                                                                                                                                                                                                                                Priority Journals
199912
                                                                                                                                                                                                                                                                                                                Netherlands
                                                                                                                                                                                                                                                                                                                                                        Goldstein B M;
                                                                                                                                                                                                                                                                                                                                                                binding.
                                                                                                                                                                                                                                                                                                                                                                                 99322380
                                                                                                                                                                                                                                                                                                                                                                                                                                                              CURRENT MEDICINAL CHEMISTRY, (1999 Jul) 6 (7) 537-43 Journal code: CO2. ISSN: 0929-8673.
                                                                                                                                                                                        131:83979
                                                                                                                                                                                                                                                         19991203
                                                                                                                                                                                                                                                                                                       Journal; Article; (JOURNAL ARTICLE)
                                                                                                                                                                                                                                                                                                                        Journal code: CO2. ISSN: 0929-8673.
                                                                                                                                                                                                                                                                                                                                                                                               ANSWER 3
                                                                                                                                                                                                                                                                                                                                                                                                                19991203
                                                                                                                                                                                                                                                                                                                                                                                                                        Priority Journals
199912
                                                                                                                                                                                                                                                                                                                                                                                                                                                        Netherlands
                                                                                                                                                                                                .999:464100
                                                                                                                                                                                                                                                                                                                                                                                                                                               Journal; Article; (JOURNAL ARTICLE)
                                                                                                                                                                                                                                                                                        REVIEW,
                                                                                                                                                                                                                                                                                                                                                                                         999322380
1998-IB2109
        1997-997758
               9915022
                                         ₩:
                                        GH,
                                                TR, KE,
                                                                                                                                                                                                                                                                                                                                                                                               OF 3
                                                                                                                                                                                                                                                                                        ACADEMIC)
                        GA R
                                                TAX SEA
                                                                                                                                                                                                CAPLUS
                                                                                                                                                                                                        CAPLUS COPYRIGHT 2000 ACS
                                                                                                                                                                                                                                                                                                                                                       Colby T D
                                                                                                                                                                                                                                                                                                                                                                                               MEDLINE
                                                                                                                                                                                                                                                                                                                                                                                         MEDLINE
                        GR KE, VO
                                                                                                                                                                                                                                                                                                 (REVIEW)
        .19971224
                                                                KP,
                                                                                                                                                                                                                                                                                                                                                                        ***dehydrogenase***
                                                                                ΑT,
19981223
                                                                                                        KIND
                                                                                        A
                       KR, KR, UG, UG, GR, GR,
                                                                                ΑU,
                                                                                                        DATE
                                                                                        19990708
                                                                AZ,
GB,
KZ,
                19990719
                                                                                                                                                                      ***dehydrogenase***
                                                                                                                                                        USA
                        MR,
                                                8 3 E 8
                        NE,
                                                Y R
                       SN,
                                                                                                                                                                                                                                                                                                                                                                       : structural aspects of inhibitor
                ΑU
                                                                                        WO 1998-IB2109
                                                                                                       APPLICATION NO.
                      TD,
                                                ¥
                                                                         S.
                1999-15022
                      TG,
                                                                                                                                                                              ***inosine***
                                                       SE,
                               SE,
                                                                         E
                                                       SG
                                                                'n
                                                                                                                                                                       ( ***IMPDH***
                                                                                                                                                                                                                                                                                                                                                                                               DUPLICATE
                               ID,
SI,
SE,
GF,
                                                                                CH,
                                                                               19981223
, CN, CU,
                                                                                                       DATE
                              BJ,
               19981223
                                                                M H
                                                        S
                               CF E
                                                                র
ন
                               유
                                                               ₩.
                               CI S I H M H H
                                                3
```

RE.CNT

Biosciences Division, Argonne National Laboratory.

(1) American Cyanamid Co; EP 0608722 A 1994
(2) Baltarini And De Clercq; BIOCHEMICAL JOURNAL 1992, V287, P785
(3) Carr; JOURNAL OF BIOLOGICAL CHEMISTRY 1993, V268(36), P27286 (4) Pankiewicz; PHARMACOLOGY AND THERAPEUTICS 1997, V76(1-3), P89
(5) Vertex Pharma; WO 9741211 A 1997 P89 CAPLUS CAPLUS

1 d kwic 1

```
ΑB
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            119
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    partial structures from eukaryotic organisms will provide an explanation of their distinct properties and contribute to the design of specific bacterial ***IMPDH*** inhibitors.
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        of the Structural Biology Center at Argonne's Advanced Photon Source.
***pyogenes***

***IMPDH*** is a tetramer with its four subunit
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           Comparison of the structure of bacterial
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        catalytic element and indicate there are significant differences in the
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             and the ***crystal*** ***structure***, we prepared several site-specific mutants to examine the role of various active site regions
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                domains: and a cystemic reprovided by sequence alignments far unknown function. Using information provided by sequence alignments and the ***crystal*** ***structure***, we prepared several and the ***crystal*** ***structure***, we prepared several
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   related by a crystallographic 4-fold axis. The protein is composed of two domains: . . . and a cystathione beta-synthase (CBS) dimer domain of so
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              between the bacterial and mammalian ***IMPDH*** enzymes, making it an attractive target for antimicrobial agents. To evaluate the basis for
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      ***IMPDH*** enzymes. However, the lack of sensitivity to mycophenolic acid and the Km for NAD (1180 microM) exemplify some of the differences between the bacterial and mammalian ***IMPDH*** enzymes, making it an
                                                                                                                                                                                                                                                                                                                                                                                                                                                     Check Tags: Support, U.S.
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             catalytic environment of bacterial and mammalian
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           site. The structure was determined using selenomethionine-substituted.
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             of the bacterial enzyme at 1.9 A with substrate bound in the catalytic
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      these differences, we determined the
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           agents, we have expressed and characterized pathogenic bacterium ***Streptococcus***
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   basis for the evaluation of
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  enzyme that catalyzes the first step unique to GTP synthesis.
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     in catalysis. These variants implicate the.
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             results show that the biochemical and kinetic characteristics of S.
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            Characteristics and
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      inosine-5'-monophosphate dehydrogenase.
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       ANSWER 1 OF 3 MEDLINE
                                                                                                                                                                                                                                                                                                                                                  Dimerization
Recombinant Proteins: GE, genetics Recombinant Proteins: ME, metabolism
                                                                                                                                                                                                                                                                                                                Enzyme Inhibitors: PD, pharmacology
                                                                                                                                                                                                                                                                                                                                                                                 Crystallography, X-Ray
                                                                                                                                                                                                                                                                                                                                                                                                                          Catalytic Domain
                                                                           Recombinant Proteins: CH,
                                                                                                             Protein Conformation
                                                                                                                                            Mutagenesis, Site-Directed
                                                                                                                                                                                 Models, Molecular
                                                                                                                                                                                                         ****IMP Dehydrogenase: CH,
*** IMP Dehydrogenase: GE,
*** IMP Dehydrogenase: ME,
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         obtained with synchrotron radiation from the undulator beamline (191D)
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    ***dehydrogenase***
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 * * * IMPDH * * *
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         ***crystal***
                                                                                                                                                                                                                                                                                                                                                                                                                                                     Gov't; Non-P.H.S
                                                                       chemistry
                                                                                                                                                                                                                metabolism***
                                                                                                                                                                                                                                               genetics***
                                                                                                                                                                                                                                                                                     chemistry***
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            * * * HDDH * * *
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           is a tetramer with its four subunits
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          are similar to other bacterial
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   ***crystal***
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             ***IMPDH*** ) is an essential
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     ***Structure***
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              malian ***IMPDH*** with
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                inhibitors as antimicrobial
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             *** IMPDH***
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    ***pyogenes***
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 flap as an essential
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       DUPLICATE 1
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           with the known
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   ***structure***
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     of bacterial
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             from the
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              To provide
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             enzymes
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               Our
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          s
```

****Streptococcus pyogenes: EN, enzymology**

=> d kwic 1 14

Н ij H Η T H ST , II T Bacillus subtilis 9028-93-7 study); BIOL (Biological study) RL: ANT (Analyte); BSU (Biological study, unclassified); ANST (Analytical 118-00-3, Guanosine, biological studies Drosophila Molecular cloning Drug screening Eukaryote (Eukaryotae) Escherichia coli This invention relates to methods to identify specific inhibitors of the purine nucleotide synthesis enzyme, ***IMPDH*** . ***IMPDH*** is Neurospora Bacteria (Eubacteria) of exogenous guanosine as a control component of the methods allows for Method to identify specific inhibitors of ***monophosphate*** ***dehydrogenase other causes of decreased cell proliferation.
inhibitor ***inosine*** ***monophosphate*** the identification of inhibitors specific for host systems commonly used for the expression. the pJF118EH expression vector. A variety of eukaryotic or prokaryotic illustrate the utility of the invention, the coding sequence of human and
Streptococcus , ***pyogenes*** ***IMPDH*** were cloned i bacteria and is an important therapeutic target. an essential enzyme found in all free-living organisms from humans to ANSWER 1 OF 7 CAPLUS COPYRIGHT 2000 ACS [nsect (Insecta) dentification of specific inhibitors of any ***Streptococcus*** ***HGGWI*** (method to identify specific inhibitors of
monophosphate ***dehydrogenase*** ***monophosphate*** * * * HUGWI * * * **Streptococcus***

pyogenes

(IMP-encoding gene from; method to identify specific inhibitors of

inosine

monophosphate

dehydrogenase ***IMPDH***)) (H712, expression host; method to identify specific inhibitors of ***inosine*** ***monophosphate*** ***dehydrogenase*** (be expressed in a functional form in a recombinant host cell. BSU (Biological study, unclassified); (expression host; method to identify specific inhibitors of ***Inosine*** ***monophosphate*** ***dehydrogenase*** ***pyogenes*** ***dehydrogenase*** ***dehydrogenase*** ***monophosphate*** ***dehydr lassified); PRP (Properties); BIOL ***inosine*** ***dehydrogenase*** ***dehydrogenase*** * * * IMPDH * * * ***inosine*** ***inosine*** * * * IMPDH * * * (***IMPDH*** (***IMPDH*** (***IMPDH***)) The invention allows the . prodn. * * * IMPDH * * * ***dehydrogenase*** ***dehydrogenase** ***inosine*** were cloned into enzyme which Utilization rather than Ξ

```
a
                                                                                                                                                                AN
DN
TI
    S
                                                                                                                                                                                                                                                                                                      => d 1-3
                                                                                                                                                                                                                                                                                                                                            PROCESSING COMPLETED FOR L11

3 DUP REM L11 (0 DUPLICATES REMOVED)
                                                                                                                                                                                                                                                                                                                                                                                                                    => dup rem 111
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   => s 14 and ((crystal or x-ray or (x(w)ray)) (3w) structur?)
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        => s 14 and 17
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       SEARCH ENDED BY USER
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        => s 14 and 117
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         L3
L3
L4
L5
L6
L7
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            ij
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  d hist
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   FILES SEARCHED.
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       FILES SEARCHED...
                                                                   Center for Mechanistic Biology and Biotechnology, Argonne National
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    ---User Break---->
  BIOCHEMISTRY,
                      Fcollart@anl.gov
                                                                                           Joachimiak A; Collart F R
                                                                                                             Zhang R; Evans G; Rotella F J; Westbrook E M; Beno D; Huberman
                                                                                                                                                            Characteristics and ***crystal***
                                                                                                                                                                                       99218077
                                                                                                                                                                                                                               ANSWER 1 OF 3
                                                                                                                                      inosine-5'-monophosphate dehydrogenase
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             FILE 'MEDLINE, BIOSIS,
                                            Laboratory, 9700 South Cass Avenue, Argonne,
                                                                                                                                                                                                             1999218077
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  BIOTECHNO,
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               RL: BUU (Biological use, unclassified); BIOL (Biological study); USES
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          367-93-1
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               (FILE 'HOME' ENTERED AT 13:33:32 ON 16 OCT 2000)
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               (Uses)
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              (method to identify specific inhibitors of
***monophosphate*** ***dehydrogenase***
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   24 S PYOGENES AND L1
31 S L1 AND (STREPTCOC? OR PYOGENES)
7 DUP REM L3 (24 DUPLICATES REMOVED)
66589 S (THREE (W) DIMENSIONAL (W) STRUCTUR?) OR (3D
0 S L1 AND L2 AND L5
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    13789 S L5 AND ((CRYSTAL OR X-RAY OR (X(W)RAY)) (3W) STRUCTUR?)
18 S L1 AND L3 AND ((CRYSTAL OR X-RAY OR (X(W)RAY)) (3W) STR
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            'MEDLINE, BIOSIS, CAPLUS, EMBASE, LIFESCI, SCISEARCH, TOXLINE, CABA, CHMO, CANCERLIT, ESBIOBASE' ENTERED AT 13:33:43 ON 16'OCT 2000 4033 SIMPDH OR (INCSINE (M) MONOPHOSPHATE (M) DEHYDROGENASE?) OR (
                                                                                                                                                                                                                                                                                                                                                                                                                                                            3 L4 AND ((CRYSTAL OR X-RAY OR (X(W) RAY)) (3W) STRUCTUR?)
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              0 L4 AND L7
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     3 DUP REM L8 (15 DUPLICATES REMOVED)
(1999 Apr 13) 38 (15) 4691-700
                                                                                                                                                                                                                                 MEDLINE
                                                                                                                                                                                                           MEDLINE
                                                                                                                                                            ***structure***
                                     Illinois 60439-4833, USA.
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    ***inosine***
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                ( ***HMPMI***
                                                                                                                                                            of bacterial
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            (W) STRUCTUR?)
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         (3W) STRUCTU
                                                                                                               m
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                Ξ
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     OR (I
```

Journal code: AOG. ISSN: 0006-2960.

SO ΑU 112 T1 AN DN TI AN AN EW ES 35 SO SS A EW EW SS 급모 E S E E E C Ω ANSWER 3 OF 1999322380 ANSWER 2 OF 1999322381 ti au so abs have clinical utility as antiviral, anticancer or immunosuppressive enzyme of de novo guanine nucleotide synthesis. Journal code: CURRENT MEDICINAL CHEMISTRY, (1999 Jul) 6 (7) 537-43. Zhang R; Differential signatures of bacterial and mammalian ANSWER 2 OF 3 MEDLINE General Review; (REVIEW) Center, Rochester, NY, 14642, USA.. barry_goldstein@urmc.rochester.edu binding. Biosciences Division, Argonne National Laboratory. CURRENT MEDICINAL CHEMISTRY, (1999 Jul) 6 (7) 537-43. Journal code: CO2. ISSN: 0929-8673. English Journal; Article; (JOURNAL ARTICLE) Goldstein B M; 99322380 Differential signatures of bacterial and mammalian ***dehydrogenase*** enzymes. Priority Journals Netherlands Journal code: C02. ISSN: 0929-8673 Department of Biochemistry and Biophysics, University of Rochester Medical 19991203 Journal; Article; (JOURNAL ARTICLE) Netherlands Collart Zhang R; Evans G; Rotella F; Westbrook E; Huberman E; Joachimiak A; 199907 United States 99912 Priority Journals English 99322381 PDB-1ZFJ Priority Journals English REVIEW, .99912 Journal; Article; (JOURNAL ARTICLE) *** IMP* ***dehydrogenase*** ***IMP*** OF 3 Evans G; Rotella F; Westbrook E; ACADEMIC) C02. ISSN: 0929-8673. MEDLINE MEDLINE MEDLINE MEDLINE Colby T ***dehydrogenase*** ***dehydrogenase*** enzymes. structural aspects of inhibitor (***IMPDH*** Huberman E; Joachimiak A; ***IMPDH*** ***IMP*** ***IMP***) is an essential inhibitors

agents. The essential nature of this enzyme suggests its therapeutic

development of antimicrobial agents

strategies for the design of improved inhibitors.

These structures reveal enzyme-ligand

interactions which

L12 TI So ΑU C-terminal face of each barrel. The IMP base is well positioned to stack $\ensuremath{\mathsf{a}}/\ensuremath{\mathsf{b}}$ barrels, with the active site located partly at the monomer-monomer interface. The substrate and cofactor bind in a continuous cleft on the active site cleft is further bounded by a highly flexible flap and loop. against the NAD nicotinamide ring to facilitate hydride transfer. Borrelia burgdorferi enzymes. Each structure crystallizes as a tetramer of available. These include structures of the human type II, hamster, potentially more effective isoform-specific agents. Recently, a number of ***Crystal*** ***Structures*** of ***IMPDH*** have become of which suffer from some degree of toxicity and/or susceptibility to metabolic substrate site (e.g. ribavirin and mizoribine) or at the NAD site use or under development. These include agents that bind at either the Journal code: C02. ISSN: 0929-8673. CURRENT MEDICINAL CHEMISTRY, (1999 Jul) 6 (7) 519-36. binding. ANSWER 3 OF 3 sequence signatures identified by this process include regions involved subunit interactions, the active site flap and the NAD binding region. Analysis of sequence alignments in these regions indicates a pattern of the NAD-dependent oxidation of inosine 5 monophosphate (IMP) to xanthosine Goldstein B M; signature will Elucidation of the basis for this mammalian/bacterial amino acid conservation associated with the major phylogenetic groups. catalytic residues conserved in all enzymes and a secondary pattern of the bacterial and mammalian those likely to have a role in catalysis using information derived from fritrichomonas foetus, inactivation. The finding that rational (mycophenolic acid and thiazole-4-carboxamide adenine dinucleotide). enzyme. We used sequence alignments of this mammalian or bacterial enzyme signature is a prerequisite for the consequence of the variance of specific, kinetic differences between bacterial and mammalian enzymes are a enzymes, suggesting characteristics that are different than the mammalian dentify sequence signatures associated with bacterial or eukaryotic dentification of these residues or combination of residues that impart monophosphate. Several classes of ***IMPDH*** ***Inosine*** * * * 4 MP * * * ***structures*** * * * HDGMI * * * antileukemic and immunosuppressive therapy. re will provide insight into the catalytic mechanism of this enzyme foundation for the development of highly specific inhibitors. tion. The finding that ***IMPDH*** exists as two isoforms, one (type II) is induced in tumor cells, has led to the search for identification of agents that specifically target the bacterial of antimicrobial agents. We suggest that the biochemical and * * * HDGMI * * * MEDLINE , E.C. 1.1.1.205) is recognized as an important target nic and immunosuppressive therapy. ***IMPDH*** catal Colby T D enzymes. These selections were further refined to discern ***dehydrogenase*** ***monophosphate*** and site-specific mutagenesis. Candidate bacterial * * * IMPDH * * * ***Streptococcus*** enzymes show biochemical and kinetic * * * HQ Q M I * * * * * * IMPDH * * * may be an attractive target for the : structural aspects of inhibitor * * * IMPDH * * * identifiable amino acid residues. *** IMPDH*** ***dehydrogenase*** ***crystal*** ***pyogenes*** inhibitors are now Ref: proteins to *** IMPDH*** * * * HDGMI * * * catalyzes and for ä 'n